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ORIGINAL RESEARCH

Outcomes Following Implantation of Two Second-Generation Trabecular Micro-Bypass Stents in Patients with Open-Angle Glaucoma on One Medication: 18-Month Follow-Up

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ABSTRACT

Introduction: The study objective was to evaluate the intraocular pressure (IOP) and medication-lowering effect of 2 second-generation trabecular micro-bypass

stents in eyes with open-angle glaucoma (OAG) on one preoperative medication.

Methods: Fifty-seven qualified phakic eyes with OAG on 1 medication, preoperative medicated IOP of 18–30 mmHg, and preoperative unmedicated (post-washout) IOP of 22–38 mmHg underwent implantation of 2 second-generation trabecular micro-bypass stents in a standalone procedure. Evaluations included IOP, best-corrected visual acuity, medication use, fundus and slit lamp examinations, visual field, cup to disc ratio, pachymetry, and complications and interventions. Subjects have been followed for 18 months, and follow-up is ongoing.

Results: At Month 12 postoperative, 100% of eyes had achieved an IOP reduction $\geq 20\%$ (100% had IOP ≤ 18 mmHg and 67% had IOP ≤ 15 mmHg) without medication versus preoperative unmedicated IOP, and 75% had IOP reduction $\geq 20\%$ without medication versus preoperative medicated IOP. The Month 12 mean unmedicated IOP had decreased by 42%, to 14.2 ± 1.9 mmHg vs 24.4 ± 1.3 mmHg preoperatively, and this reduction was maintained through 18 months (14.4 ± 2.1 mmHg). A high safety profile was observed.

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Conclusion: In this prospective, open-label, single-arm study, the standalone implantation of two second-generation trabecular micro-bypass stents in OAG patients on 1 preoperative medication resulted in IOP reduction to ≤ 15 mmHg and elimination of medication through 18 months, with favorable safety.

Trial Registration: ClinicalTrials.gov identifier, NCT02868190.

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Keywords: Glaucoma; IOP; Medication; MIGS; Ophthalmology; Trabecular micro-bypass

INTRODUCTION

The most important risk factor for glaucoma, the leading cause of permanent blindness worldwide [1], is elevated intraocular pressure (IOP). Thus, a central goal of all glaucoma therapy is IOP reduction, which can be achieved through pharmacologic, laser, or surgical means. Traditionally, trabeculectomy has been considered the gold standard of glaucoma surgery, but typically it has been reserved for more advanced stages of the disease [2]. Over the past decade, the development of microinvasive glaucoma surgery (MIGS) procedures has increased the surgical options available to clinicians treating mild to moderate open-angle glaucoma (OAG). The first FDA-approved MIGS device, the first-generation iStent (iStent® Trabecular Micro-Bypass, Glaukos Corporation, San Clemente, CA, USA), is a single-piece titanium stent designed to bypass the main site of aqueous fluid outflow resistance in OAG, the trabecular meshwork, with minimal trauma to intraocular and extraocular structures. A

substantial body of literature has shown that *ab interno* implantation of these stents can reduce IOP and medication burden for up to 5 years postoperatively in patients with mild to moderate OAG. Key studies have evaluated outcomes after implantation of single [3–6] and multiple [7] iStent devices during cataract surgery, and with multiple iStent devices as a standalone procedure [8–11].

More recent years have brought the advent of second-generation trabecular micro-bypass stents (iStent *inject*® Trabecular Micro-Bypass, Glaukos Corporation, San Clemente, CA, USA). Several studies have demonstrated substantial IOP and medication reduction following implantation of 2 iStent *inject* devices during cataract surgery [12] or in standalone procedures [13–16]. In addition to their clinical effectiveness, these devices have shown a favorable safety profile, which is an important advantage over traditional surgeries such as trabeculectomy or tube placement, or more recently developed suprachoroidal stents [17, 18].

In the present study, we tested the hypothesis that IOP and medication burden would be reduced following the standalone implantation of 2 second-generation iStent *inject* devices in eyes with OAG not controlled on 1 preoperative medication, while maintaining favorable safety parameters. This report covers outcomes in 57 eyes through 18 months postoperation, and follow-up is continuing through 5 years.

METHODS

This was a prospective, unmasked, single-arm study designed to enroll phakic or pseudophakic (with posterior chamber intraocular lens) subjects with OAG, medicated

IOP at screening of 18–30 mmHg on 1 topical ocular hypotensive medication, and unmedicated (post-washout) IOP of 22–38 mmHg. Medication washout included 5 days for carbonic anhydrase inhibitors, 2 weeks for alpha agonists, and 4 weeks for beta blockers and prostaglandin analogues. Subjects were to have cup to disc (C:D) ratio of ≤ 0.9 , best-corrected visual acuity (BCVA) of 20/100 or better, and normal angle anatomy. Exclusion criteria included pseudoexfoliative, pigmentary, uveitic, traumatic, neovascular, or angle-closure glaucoma; glaucoma associated with vascular disorders; and prior glaucoma surgery of any kind.

This single-site study was conducted at the S.V. Malayan Ophthalmological Center in Yerevan, Armenia. All surgeries were performed by the staff surgeon (L. Voskanyan) and 10 visiting surgeons from the MIGS Study Group (Supplementary Material—Appendix 1). Pre- and postoperative examinations were completed by glaucoma-trained ophthalmologists at the Center. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study. The ClinicalTrials.gov registration number for this study is NCT02868190.

As described previously in detail [12–15], the second-generation iStent *inject* device is a single-piece, titanium, heparin-coated stent with 360 μm length, 230 μm maximum width, and multiple lateral outlet lumens to facilitate aqueous fluid outflow (Fig. 1). Two stents are pre-loaded in a single disposable stainless steel inserter, which is advanced *ab internally* through a temporal clear corneal incision to implant 2 stents through the trabecular meshwork into the nasal Schlemm's canal at approximately 2 clock-hours apart. The bypassing of the trabecular meshwork is designed to promote aqueous outflow and thereby decrease IOP. Using this technique, all subjects had implantation of 2 iStent *inject* devices in the nasal Schlemm's canal at approximately 2 clock-hours apart. Postoperatively, patients received topical anti-infective medication (for 1 week) and anti-inflammatory medication (for 4 weeks).

Efficacy and safety evaluations included IOP measurement (Goldmann applanation tonometry), BCVA (Early Treatment Diabetic Retinopathy Study scale), slit lamp biomicroscopy, indirect ophthalmoscopy, C:D ratio, visual field (Swedish Interactive Thresholding Algorithm Standard 24-2 automated perimetry), pachymetry, medication use, and ocular complications and secondary surgical interventions. Postoperative examinations occurred at Day 1; Week 1;



iStent *inject* stents



iStent *inject* Trabecular Micro-Bypass Stent System

Fig. 1 The iStent *inject* and iStent *inject* trabecular micro-bypass stent system

Months 1, 3, 6, and 12; and are planned for every 6 months, thereafter until Month 60. Additional ocular hypotensive medication was to be started if postoperative IOP exceeded 21 mmHg at any postoperative visit, and/or in the case of concerning optic nerve findings, at the discretion of the investigator.

The primary efficacy endpoint was the proportion of patients with a Month 12 mean unmedicated IOP reduced by $\geq 20\%$ versus baseline unmedicated IOP. The secondary efficacy endpoints included the proportion of patients with Month 12 IOP of ≤ 18 or ≤ 15 mmHg without medications; and the proportion of patients with Month 12 IOP reduced by $\geq 20\%$ without medication versus baseline medicated IOP. Proportional analyses were performed for the primary and secondary efficacy endpoints. For continuous variables, mean and standard deviation values were calculated. Statistical tests were performed using software from the R Project for Statistical Computing (version 3.1.3, The R Foundation, Vienna, Austria).

RESULTS

Subject Accountability, Demographics and Pre-Study Parameters

A total of 57 qualified subjects underwent *ab interno* implantation of 2 iStent *inject* devices in a standalone procedure (i.e., without cataract surgery). Table 1 shows demographic and preoperative parameters. Mean age was 65.3 ± 9.0 years, with approximately equal gender distribution. All subjects were phakic. Preoperative mean medicated IOP was 19.5 ± 1.5 mmHg on 1 medication, and mean unmedicated (post-washout) IOP was 24.4 ± 1.3 mmHg. Subjects have been followed for 18 months, and follow-up is ongoing.

Table 1 Subject demographic and preoperative characteristics ($N = 57$)

Total	57 eyes of 57 subjects
Gender	
Male/Female	30/27
Race	
Caucasian	100% ($n = 57$)
Age (years)	
Mean \pm SD	65.3 ± 9.0
Preoperative cup-to-disc (C:D) ratio	0.7 ± 0.1
mean \pm SD	
Preoperative medicated IOP (mmHg)	19.5 ± 1.5
mean \pm SD	
Preoperative # medications	
Mean \pm SD	1 ± 0
Type of medications	
Prostaglandin	86% ($n = 49$)
Beta-blocker	7% ($n = 4$)
Carbonic anhydrase inhibitor	7% ($n = 4$)
Preoperative unmedicated IOP (mmHg) mean \pm SD	24.4 ± 1.3

IOP intraocular pressure, SD standard deviation

Efficacy

Figure 2 shows a proportional analysis of IOP at Month 12, and Fig. 3 shows the mean IOP over time for the 18-month period after stent implantation ($N = 57$). At Month 12, 100% of eyes had achieved an IOP reduction $\geq 20\%$ (100% had IOP ≤ 18 mmHg and 67% had IOP ≤ 15 mmHg) without medication versus preoperative unmedicated IOP, and 75% had IOP reduction $\geq 20\%$ versus preoperative medicated IOP. At Month 18, mean unmedicated IOP had decreased 41% versus preoperative unmedicated IOP (to

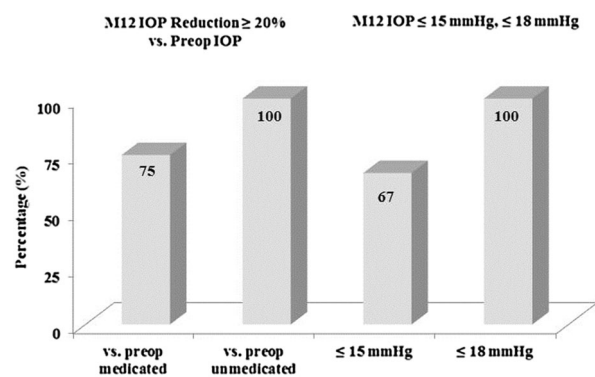


Fig. 2 Proportional analysis of Month 12 intraocular pressure (IOP) ($N = 57$). *M* month

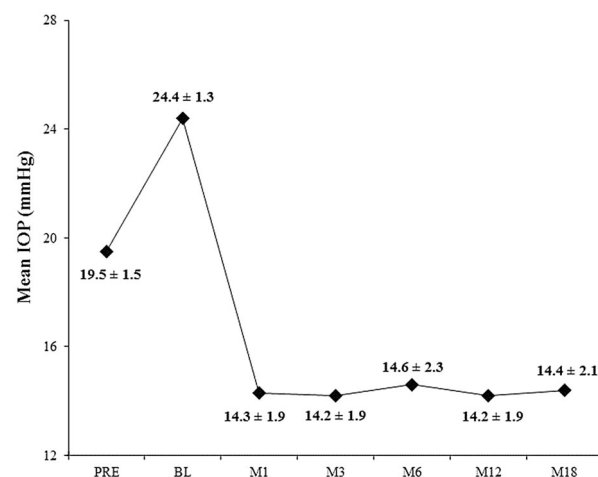


Fig. 3 Mean intraocular pressure (IOP) over time ($N = 57$). *BL* baseline, *M* month, *PRE* preoperative

14.4 ± 2.1 mmHg from 24.4 ± 1.3 mmHg preoperatively); and had decreased 27% versus preoperative medicated IOP (19.5 ± 1.5 preoperatively). One subject was placed on a medication at Month 18 for optic nerve findings (IOP was 17.7 mmHg), but all remaining subjects remained off medications.

Safety

All subjects underwent uncomplicated *ab interno* placement of 2 iStent *inject* devices in a standalone procedure, with no intraoperative

adverse events observed. Postoperatively, 1 subject had progression of preexisting cataract with corresponding BCVA loss >1 line. BCVA has been stable over time for the remaining subjects (93% with Month 18 BCVA 20/40 or better and 98% with BCVA 20/100 or better) (Fig. 4). The mean C:D ratio, visual field mean deviation and pattern standard deviation, and central corneal thickness also remained stable over the 18-month follow-up (Table 2).

DISCUSSION

Data from this prospective study confirm the hypothesis that phakic subjects with OAG and on 1 ocular hypotensive medication can successfully and safely achieve sustained IOP and medication reduction following implantation of two second-generation iStent *inject* devices as a sole procedure. Specifically, a $\geq 20\%$ IOP reduction with elimination of medication was achieved in all subjects at 12 months, with all patients maintaining IOP of ≤ 18 mmHg and two-thirds reaching IOP of ≤ 15 mmHg. At Month 12, the mean unmedicated IOP had decreased by 42%, to 14.2 vs 24.4 mmHg preoperatively, and this reduction was maintained through 18 months (14.4 mmHg).

These outcomes corroborate the considerable existing body of research showing substantial IOP and medication reduction and favorable safety of *ab interno* trabecular micro-bypass implantation in patients with mild to moderate glaucoma. Prior studies have evaluated single [3–6] and multiple [7] first-generation stents (iStent) during cataract surgery; multiple first-generation stents as a standalone procedure [8–11]; and two second-generation stents (iStent *inject*) either with [12] or without cataract surgery in OAG

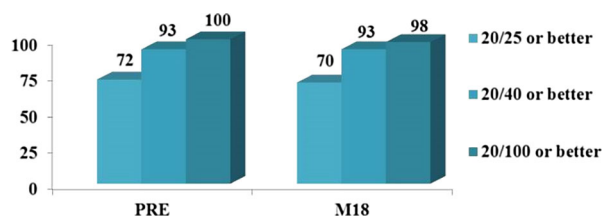


Fig. 4 Preoperative and Month 18 best-corrected visual acuity (BCVA) ($N = 57$). *M* month, *PRE* preoperative

patients with moderate IOP elevation and/or medication burden [13–16]. In the present study, the observed IOP reduction of 10.2 mmHg was similar to the 7.0–10.5 mmHg reduction observed in these earlier studies of standalone iStent *inject* implantation in phakic eyes with OAG [13–16]. The present study analyzes IOP and medication use after standalone iStent *inject* implantation in phakic OAG eyes with IOP not managed to below 18 mmHg on 1 preoperative medication. Thus, the findings shed light on the utility of these stents in a relatively early stage of managing the disease.

The reduction in medication-free IOP supports the independent effect of second-generation trabecular micro-bypass stents without the confounding factors of concomitant cataract surgery or medication use. Perhaps even more meaningful, subjects' postoperative IOP was 27% lower without

medications 18 months after receiving 2 iStent inject devices than with medication before surgery. The elimination of medication represents a benefit in terms of both cost [19] and compliance [20–23] to glaucoma patients, most of whom have at least one other chronic condition demanding their funds and attention [24]. Indeed, an inherent advantage of *ab interno* trabecular bypass stents over medications is reduced dependence on medication compliance, which theoretically may increase long-term treatment success.

Safety outcomes were favorable through the 18 months of follow-up, with only 1 postoperative adverse event (BCVA loss due to cataract progression; cataract surgery has been planned) and no intraoperative or device-related adverse events. Furthermore, the study's involvement of multiple surgeons offers external validation of safety of the implantation technique. This favorable safety profile is consistent with that observed in previous studies of iStent *inject* in subjects with mild to moderate primary OAG [12–16]. One additional medication was started in 1 eye at 18 months (IOP was 17.7 mmHg), but all remaining eyes remained medication-free, and no eyes underwent secondary surgery. Subject accountability was 100% through 18 months, supporting the validity of the study's findings.

Table 2 Screening and postoperative mean cup-to-disc (C:D) ratio, visual field (VF), and central corneal thickness, available eyes at each visit

	Screening	M6	M12	M18
<i>N</i>	57	57	57	57
C:D ratio mean (SD)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)
VF—mean deviation (dB) mean (SD)	−4.9 (5.3)	−4.8 (5.3)	−4.5 (5.1)	−4.5 (5.2)
VF—pattern standard deviation (dB) mean (SD)	3.3 (2.4)	3.1 (2.3)	3.1 (2.3)	3.0 (2.3)
Corneal thickness (μm) mean (SD)	544.9 (30.3)	546.1 (30.0)	545.6 (29.9)	545.4 (29.7)

M month, *SD* standard deviation

This is a nonrandomized, open-label, single-arm study with several limitations which may be noted. The study's single-site design prevents a consideration of site-specific effects or measurement variability as potential confounders. Since multiple IOP readings were not taken, regression to the mean is a possibility. Because stent implantation was completed as a standalone procedure in this study, a sham surgical control group (consisting of merely injecting and removing viscoelastic) was not considered for ethical reasons. However, we considered it reasonable that patients' preoperative data served as their own control. The patient population was 100% Caucasian and included only phakic eyes, making it impossible to stratify by race or lens status. IOP measurements at multiple time points were not taken for every visit, diurnal IOP was not measured, and standardized preoperative grading of the crystalline lens was not completed.

CONCLUSIONS

This study collected valuable data in a stable cohort with excellent accountability through 18 months, and follow-up is ongoing. The results confirm that IOP reduction to ≤ 15 mmHg with elimination of medication—and a favorable safety profile—is possible after the standalone implantation of two iStent *inject* devices in OAG eyes with IOP not managed to below 18 mmHg on 1 preoperative medication. In light of this positive benefit-to-risk profile, as well as the well-known issues with compliance, cost, and side effects associated with topical medications, this microsurgical technique may constitute a desirable alternative for these patients with earlier stages of OAG.

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Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

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